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Case Report

Probable Case of Cutaneous Anthrax with Toxic Manifestations and Fatality seen in an adolescent in Sokoto, Nigeria: A post-mortem review

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Abstract

Background: Anthrax is a life-threatening zoonotic disease caused by Gram-positive, spore-forming bacterium *Bacillus anthracis*. It manifests as a cutaneous, gastrointestinal, and respiratory disease. The cutaneous form ranges from a self-limiting lesion to severe edematous lesions with toxemic shock. Of recent, increasing cases of anthrax have been reported in Nigeria warranting heightened surveillance. A patient with skin lesions suggestive of cutaneous anthrax and toxic manifestations is reviewed to emphasize the need for a high index of suspicion.

Case report: A 14-year-old boy presented with skin lesions of one month involving the hands, face, and legs, left lower limb swelling of two weeks, fever of 10 days, and fast breathing of five days duration. There was a positive history of contact with cattle carcasses at the abattoir. He was febrile (38.1^{o}c), mildly pale, and mildly dehydrated, oxygen saturation was 95%. He was tachypnoeic and tachycardic with a low-volume pulse. There was extensive left lower limb swelling, a raised necrotic ulcer with a black surface on the calf, measuring 9cmx5cm with serosanguinous discharge, and another confluent vesicular lesion on the anterolateral aspect of the left leg measuring 8cmx6cm. Differential diagnoses considered were cellulitis, osteomyelitis, leishmaniasis, and malignancy.

Result, treatment & outcome: His packed cell volume was 33%, retroviral screening, and hepatitis screening were non-reactive, and erythrocyte sedimentation rate was 3mm/hr. Leg X-ray was normal. Other investigations could not be done due to financial constraints and the patient's demise. He received intravenous (IV) fluid, IV ceftriaxone, IV metronidazole, tetanus toxoid, and antiseptic wound dressing. He succumbed to the illness 72 hours later. Anthrax was considered after the patient's demise due to the type of skin lesion and progression of the illness in line with the standard case definition.

Conclusion: Cutaneous anthrax with systemic manifestations should be considered as a probable diagnosis in patients with typical skin lesions and toxic features.

Keywords: *Cutaneous Anthrax; Toxic; Mortality; Adolescent; Sokoto; Nigeria.*

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Introduction:

Anthrax is a life-threatening zoonotic disease caused by Gram-positive, spore-forming bacterium Bacillus anthracis. The disease mainly affects herbivorous animals both wild and domestic. The organism secondarily infects humans through contact with infected animals, their carcasses, and their products. The organism exists in 2 forms, biologically active vegetative form and inert spore forms. The spores can also be directly inhaled and cause infection in men.[1] These spores contaminate soil mainly, but also grass and water sources. They are highly resistant to heat, pressure, radiation, chemical agents, and disinfectants and, therefore, are prime targets for use as biological agents for bioterrorism.[2]

Human anthrax is categorized as agricultural or industrial in origin. The agricultural form is endemic in animals in low- and- middle-income countries with infection occasionally affecting humans. The industrial form is from occupational exposure to animal products. Epidemiologically, it is classified as naturally occurring anthrax and bioterrorism-related anthrax. Most cases are naturally occurring, and it is endemic in parts of Asia, Central America, and West Africa.[1]

This disease dates back to centuries ago and has been known by several names throughout history which were related to the clinical features (malignant pustule) or affectation of some occupational group (wool sorter's disease).[3] However, some recent publications have highlighted human disease re-emergence from different regions of the world warranting more knowledge on its presentation and outcome among physicians and populace.[1,2,4,5] They have also highlighted the importance of the threat posed by transboundary animal diseases and the necessity of the WHO's One Health initiative in its holistic prevention and control.[6] A recent animal outbreak was reported in Nigeria and Ghana in mid-2023, following which there was a heightened awareness of the transmission, presentation, and complications of the disease in thesecountries.[7-9]

Most cases of human anthrax are cutaneous (95%), others are inhalational (5%), gastrointestinal (<1%), and injection anthrax occurs in intravenous (IV) drug users. The cutaneous form ranges from a self-limiting lesion to severe oedematous lesions with toxemic shock.[10] It has been recognized from the literature that cases of cutaneous anthrax may be initially missed.[10] This is because they are not common and sporadic cases of anthrax are easily overlooked and hence the diagnosis is often not considered.

A male adolescent seen in Sokoto with skin lesions highly suggestive of cutaneous anthrax, toxic manifestations, and fatality is reported to emphasize the need for a high index of suspicion with current re-emergence.

Case definitions

These have been defined by the Center for Disease Control[11] and details below were by the Ministry of Labour, Health & Social Affairs of Georgia, United States in 2016.[12]

A suspected case of cutaneous anthrax is defined as a patient with an acute illness with a painless primary skin lesion surrounded by localized or extensive edema in one of the following stages: papule, vesicle, pustule (hemorrhagic), ulcer (flat, dry, with solid black eschar on the bottom, located on the infiltrated basement and surrounded by hyperemic areola), painless solid black eschar.[12, 13]

A probable case of cutaneous anthrax is defined as a patient who satisfied the criteria for a suspected anthrax case and at least one of the following[12, 13]

i. Within two weeks of the onset of symptoms, travelled to or resided in an area where cases of animal or human anthrax were reported
ii. handled animal products (meat, skin, leather, or bones); consumed raw or undercooked meat.
iii. cleaned farms or areas where agricultural animals are/were kept.

iv. got bit by large, blood-sucking insects (horseflies).
v. performed work involving soil in an area where sick animals were stored or buried.
vi. gram-positive capsule and/or spore-developing bacillus detected in a microscopic examination
vii. a positive response to an allergic skin test in individuals who have never had an anthrax vaccination or illness history.[12, 13]

A confirmed case of cutaneous anthrax is defined as a probable/suspected case with culture and identification of *B. anthracis* from clinical specimens or positive PCR results.[12, 13]

A rejected case of cutaneous anthrax is defined as a clinically compatible case without an epidemiological link and with negative laboratory results.[12, 13]

Case report

S.M, is a 14-year-old male senior secondary school student who resided with his parents in a village in Sokoto State. He presented with a history of skin rashes which initially involved the hands, face, and legs a month prior to the presentation. It worsened on the left lower limb and was associated with swelling for two weeks, and was associated with fever for fourteen days, and fast breathing for five days.

The skin lesions started on the face and hands a month prior, were small and nodular but later ulcerated with minimal discharge. They healed up after two weeks with minimal scarring. However, a similar lesion over his left calf noticed about the same time persisted. It started as a firm nodule which was pruritic & slightly hyperpigmented. It progressively increased in size over two weeks with the subsequent development of a blister that later ruptured & ulcerated. The ulcer had been discharging serous fluid, also with dark and raised edges. There was no associated pain. Swelling of the left leg started around the lesion about two weeks after its onset. It progressed to involve the other parts of the leg and the thigh. No swelling in any other part of his body. The fever, which was high-grade and persistent, started four days after the onset of the leg swelling. He developed fast breathing five days prior to the presentation. There was associated orthopnea & easy fatigability with generalized body weakness. He presented at an Infectious Disease Clinic at the onset of leg swelling, where he was placed on some oral medications. He was referred to Usmanu Danfodiyo University Teaching Hospital, Sokoto one week later due to worsening of the swelling.

He was the 4th of seven children of a 53-year-old mother who is a trader with no formal education. Father is a 70-year-old retired clerical staff with a secondary level of education. The family rears sheep and goats at home, and he usually has close contact with them. There is a positive history of frequent contact with cow carcasses in the abattoir where his older brothers worked. No history of similar illness in any other member of the family or individual in their vicinity. No history of recent travels.

On examination at presentation, he was acutely ill-looking (tachypneic), febrile (38.1^{o}C– axillary), moderately pale, mildly icteric, acyanosed, moderately dehydrated, with left inguinal lymphadenopathy, left unilateral non- pitting pedal oedema up to the thigh. Oxygen saturation in room air was 92%. There was an oval-shaped ulcer at the posterior aspect of the left leg with necrotic raised edges & scanty serous fluid discharge; measured 9cm x5cm; there was an evolving lesion superior to it. There was another confluent vesiculo-bullous lesion on the anterolateral aspect of the left leg that measured 8cm x 6cm. There was also generalized non-pitting swelling & tenderness of the whole left limb, with differential warmth and limitation of movement across the left knee & hip joints. Distal pulses were felt feebly and there was non-tender inguinal lymphadenopathy on the left. The diameter of the lower limbs at the level of tibial tuberosity was 36.5cm on the left and 26.0 cm on the right.

He was tachypneic (respiratory rate was 38breaths per minute with nasal flaring) and tachycardic (pulse rate was 136 beats per minute). There was mild epigastric tenderness with no organomegaly demonstrable per abdomen. CNS examination revealed he was lethargic and irritable with no focal deficit.

An initial diagnosis of cellulitis of the left lower limb with necrotic ulcer was made; differentials included pyomyositis of the thigh, osteomyelitis of the left tibia, cutaneous leishmaniasis, and malignancy with metastasis (soft tissue sarcomas).

Figures (1a): Showing the lesion on the posterior aspect of the left calf -known as a "malignant pustule" and a developing satellite lesion superior to it; **(1b):** Showing vesiculobullous lesions on the anterior aspect of the affected left leg; **(1c):** Showing brawny oedema of the left lower limb

Investigations & Treatment

He was admitted to the emergency unit and immediately placed on intra-nasal oxygen. He was commenced on IV Ceftriaxone, Metronidazole, intramuscular (IM) Tetanus Toxoid IV, Anti-Tetanus Serum, Tablets of Vitamin C, Vitamin B Complex, and Paracetamol. Wound toileting & dressing with povidone-iodine was also prescribed. Requested investigations included urgent packed cell volume (PCV), full blood count, erythrocyte sedimentation rate (ESR), blood film for malaria parasite (MP), retroviral screening (RVS), wound swab microscopy, culture and sensitivity (MCS). X-ray of the lower limbs, chest X-ray, and wedge biopsy of the lesion edges.

Available investigation results were PCV:33%, ESR: 13mm/hr. HIV and HBsAg were non-reactive. X-ray of the lower limbs: showed soft tissue swelling of the left lower limb with no bony involvement. Other investigations were not done due to financial constraints.

Outcome

There was no significant change in the patient's clinical status on days two and three. He became progressively irritable and delirious. At that point, he went into shock as his pulse was thready and his blood pressure reading was unrecordable except by palpation at 70mmHg. Efforts to resuscitate him proved abortive and he eventually succumbed to the illness by 72 hours on admission before a biopsy could be done.

A post-mortem review with the medical microbiologists suggested the following differentials: cutaneous anthrax, cutaneous leishmaniasis, *Pseudomonas* infected wound, malignancy of the skin (melanoma; squamous cell carcinoma), Buruli ulcer, mycetoma, chronic osteomyelitis, and cellulitis. However, the diagnosis of cutaneous anthrax was entertained on account of the striking skin lesions and the course of patients' problems before demise which suggested toxemia with shock. Efforts were made to contact the caregivers and an additional history of frequent contact with cattle carcasses was obtained.

Ethical considerations

This was sought and obtained from the Usmanu Danfodiyo University Teaching Hospital Research and Ethics Committee with approval number UDUTH/HREC/2024/1449/V1. Consent was sought from the caregivers before publication. All identifying information was removed from the images and results presented.

Discussion

Human anthrax occurs mainly in countries that do not prevent industrial or agricultural exposure to infected animals or their products like hides, carcasses, and hair including Nigeria. The period this patient was seen(July 2023) coincided with the period an outbreak was reported in Nigeria(July 2023) precisely in Niger state which is a neighbouring State to Sokoto where the patient resided.[9] In addition, there was a positive history of exposure to cattle carcasses in the patient as he frequently visited and worked in the abattoir. Cutaneous anthrax should be considered in any patient with a painless ulcer or black eschar who has a history of exposure to animals. Humans are relatively resistant to cutaneous invasion by B. anthracis, but the organisms may gain access through microscopic or gross breaks in the skin.[10]Multiple logistic regression analysis of the risk factors for human cutaneous anthrax surveillance data from 2011–2015 showed the significant association of human cutaneous anthrax with the handling of animal products with the highest adjusted Odds' ratio of 4.36 compared to the other risk factors such as living near pastoralist routes (2.74) and travelling to endemic areas within two weeks of onset (2.32).[13]

When the index patient presented with 'strange' looking lesions with marked limb oedema, it was perplexing to the managing team. It was after his demise that the case was thought to be anthrax. Doganay,[14] an author from Turkey who has written extensively on cutaneous anthrax has observed that old physicians are more familiar with clinical forms of anthrax unlike their younger counterparts, and linked this to delay in diagnosis both in endemic and Western countries.

The patient presented with marked involvement of the lower limb. This is unlike in the literature where most affected parts in cutaneous anthrax are exposed areas like the hands, arms, face, and neck.[1, 14, 15] This is due to the frequency of contact with the causative agent in those areas when handling animal products, unlike the lower limb. However, this case had some previous skin lesions on the face and hands which had healed with minimal scars before presentation. It is also possible that those initial lesions were also those of cutaneous anthrax as they were said to be of a similar nature to those that persisted on the lower limb at onset. It has been reported that mild cutaneous anthrax lesions can be self-limiting and heal without scarring possibly explaining the initial lesions he had on the face and hands.[14] However, severe cases may leave deep tissue necrosis and require reconstructive surgery.[16, 17]In a review of 15 cases of cutaneous anthrax by Yu,[15]in Shandong, China, 14 cases had affected sites on the upper limb while only one case was on the lower limb. A similar finding of only one case of lower limb involvement was reported by Doganay[17] in a review from Turkey.

The index patient had lesions that began as papulonodular lesions with progressively worsening leg swelling and areas of blistering which are typical of anthrax as described in the literature. The lesion begins as a painless, pruritic, red-brown papule that forms 1 to 10 days after exposure to infective spores. The papule enlarges with a surrounding zone of brawny erythema and marked edema. Vesiculation and

induration are present. Central ulceration follows, with serosanguineous exudation and formation of a black eschar (the malignant pustule or carbuncle).[2, 10]Local lymphadenopathy is common which the patient had at the left inguinal region. Other symptoms of cutaneous anthrax present were fever, malaise, myalgia, and headache.

Most patients with cutaneous anthrax present within 1 to 6 days of exposure, but for inhalation anthrax, the incubation period can be > 6 weeks.[10] His incubation period was not known and there was a time lag before epidemiological investigations took place which was probably responsible for the negative results. This case was a child who should not even be in an abattoir as he was a minor and less likely to be aware of risks in his surroundings. Most of the cases seen in the literature are actually young adults and males.[1, 5, 13, 15, 16]

The clinical presentation of cutaneous anthrax depends on the virulence of *B. anthracis* which is in turn influenced by the bacterial capsule and the toxin complex. The capsule is a poly-D-glutamic acid that protects against leukocytic phagocytosis and lysis. Anthrax toxins are composed of 3 entities: protective antigen, lethal factor, and oedema factor. The edema factor results in the formation of edema toxin; the binding of lethal factor results in the formation of lethal toxin. Edema toxin acts by converting adenosine triphosphate (ATP) to cyclic adenosine monophosphate (cAMP), leading to cellular oedema within the target tissue. The lethal factor is not well understood; it may inhibit neutrophil phagocytosis, lyse macrophages, and cause the release of tumor necrosis factor and IL-1. Death from anthrax occurs as a result of the effects of lethal toxin.[10, 14]

In the diagnosis of cutaneous anthrax, occupational and exposure history is important. Confirmatory investigations include Gram stain and culture, direct fluorescent antibody (DFA) test, and polymerase chain reaction (PCR) assay. However, these could not be done in our patient. Without treatment, up to 20% of cutaneous skin infection cases progress to toxemia and death.[10, 14] This is probably what our patient unfortunately had. Treatment is using antibiotics such as amoxycillin (for penicillin-susceptible strain), others are ciprofloxacin, vancomycin, carbapenems, rifampicin, clindamycin, linezolid or aminoglycoside. Other supportive care required depends on the presentation. In this case, our patient received a cephalosporin- ceftriaxone, which is not among the recommended antibiotics.

Our patient likely had a severe form of cutaneous anthrax with toxaemic shock because as described in the literature,[18] his course depicts that presentation. Mild cutaneous anthrax is characterized by the presence of a cutaneous lesion with <4cm diameter, which is surrounded by erythema, but without systemic symptoms.[19] Severe form of anthrax is defined by the presence of a large cutaneous lesion, which is surrounded by a ring of blisters with serous fluid and an area of edema that may become extensive. The lesion is often described as a "malignant pustule" due to its distinctive look.[19] Systemic symptoms include fever, tachycardia, hypotension, regional lymphadenopathy, and tachypnea.[18-20] Complications, such as toxemic shock and meningoencephalitis can occur with a mortality rate of 100% without treatment.[19,20] Another complication which is also life-threatening but rare is the compartment syndrome characterized by increased intra-compartmental pressure with damage to the vascularization of the affected limb segment, clinically characterized by pain, pallor, paresthesia, pulselessness, and paralysis.[16]In our patient, the distal pulses were feeble at a point however, this complication was not sought until the time of his demise, emphasizing the need for a high index of suspicion. This complication was thoroughly described in a case series by Pertea.[16]

In order to enhance diagnosis and prevent delays in treatment and complications, case definitions have been developed.[13,16,21,22] A probable case of anthrax is an individual person who had direct contact with sick or dead animals or their products (meat, fur, skin, etc.) or ingested their meat, or a person who inhaled dust-contaminated with BA spores or injected himself with drugs contaminated with anthrax.[21]Patients with such exposure then present with macules, itchy, painless papules, located on the chest, face, and limbs. These lesions become blisters with edema, and/or erythema, they also ulcerate

with eschars and increase in size over a relatively short time.[22] This is similar to how the index patient presented even though not confirmed. However, a confirmed case of anthrax is one in which *B. anthracis* is isolated in cultures or during PCR testing.[16, 21]

By way of prevention, controlling animal anthrax reduces the potential danger to humans since cases of naturally occurring human anthrax are almost always associated with direct contact with infected animals or their byproducts as in this case.[23] This is by implementing regular preventative vaccinations for animals. When there is an outbreak, additional control strategies such as quarantine measures, involve restricting animal movement from affected and surrounding areas and limiting animal contact. Adequate laboratory capability is essential for the early detection of an outbreak at all levels, especially at the localities. Also, in an outbreak, coordination needs to be strengthened between human health and veterinary departments as outlined by the "One Health" approach which involves active surveillance, animal vaccination, interdepartmental coordination, capacity building of various stakeholders via training, information education communication, and behavioral change communication.[5-8, 23]

Conclusion

This was an unfortunate case of a child with suspected cutaneous anthrax that was missed and eventually died during the period the anthrax outbreak was reported in Nigeria. There should be a high index of suspicion with current re-emergent outbreaks worldwide. Continuing education of the multidisciplinary teams under the "One Health" approach should be emphasized for early recognition, treatment, and control of both human and animal cases. There should be provision for both human and animal post-exposure prophylaxis and vaccines for the prevention of anthrax as well as awareness and health education of masses, especially health workers and high-risk individuals.

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Conflicts of interest: None declared

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